

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁴ :		A1	(11) International Publication Number: WO 88/00040
A61K 7/06, 31/54, 31/40			(43) International Publication Date: 14 January 1988 (14.01.88)
(21) International Application Number:	PCT/US87/01575		20 January 1987 (20.01.87)
(22) International Filing Date:	2 July 1987 (02.07.87)		20 January 1987 (20.01.87)
(31) Priority Application Numbers:	881,233 883,671 883,681 883,679 883,678 883,680 883,682 883,683 004,455 004,457 004,458 004,459 004,460 004,461 004,462		20 January 1987 (20.01.87)
(32) Priority Dates:	2 July 1986 (02.07.86) 9 July 1986 (09.07.86) 9 July 1986 (09.07.86) 20 January 1987 (20.01.87) 20 January 1987 (20.01.87) 20 January 1987 (20.01.87) 20 January 1987 (20.01.87)		(33) Priority Country: US
			(71) Applicant: AMERICAN HEALTH PRODUCTS CORPORATION [US/US]; 200 South Biscayne Boulevard, Miami, FL 33131 (US).
			(72) Inventors: FROST, Phillip ; 200 South Biscayne Boulevard, Miami, FL 33131 (US). FISHMAN, Jack ; 876 Park Avenue, New York, NY 10028 (US).
			(74) Agents: WEGNER, Harold, C. et al.; Wegner & Bretschneider, P.O. Box 18218, Washington, DC 20036 (US).
			(81) Designated States: AT (European patent), BE (European patent), CH (European patent), DE (European patent), DK, FI, FR (European patent), GB (European patent), IT (European patent), JP, KR, LU (European patent), NL (European patent), NO, SE (European patent).
			Published <i>With international search report.</i>

(54) Title: TOPICAL HAIR GROWING COMPOSITION AND KIT

(57) Abstract

A method for enhancing growth of fine vellous hair into terminal hair in an at least partially bald person which comprises topically applying to the scalp a compound selected from the group consisting of 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide, 6-chloro-3-(dichloromethyl)-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide, 2-chloro-5-(1-hydroxy-3-oxo-1-isoindolinyl)benzene sulfonamide, 3,4-dihydro-3-(phenylmethyl)-6-(trifluoromethyl)-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide, 6-chloro-3-(chloromethyl)-3,4-dihydro-2-methyl-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide, 6-chloro-3,4-dihydro-2-methyl-3-[(2,2,2-trifluoroethyl)thio]methyl]-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide and 6-chloro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide whereby the smooth muscles in the small blood vessels in the papilla part of connective tissue of skin that supplies the hair follicle is relaxed, thereby increasing blood flow to the hair matrix leading to the maturation of fine hairs into terminal hairs. Also provided is a topical medication and method for reversing the effects of baldness focused upon said compound as the active ingredient. A kit is provided which comprises the medication with said compound suitable for reversing the effects of baldness on the scalp of an at least partially bald subject which comprises a package including said compound and directions for administration of said compound to said scalp for the reversal of the effects of baldness.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	FR	France	ML	Mali
AU	Australia	GA	Gabon	MR	Mauritania
BB	Barbados	GB	United Kingdom	MW	Malawi
BE	Belgium	HU	Hungary	NL	Netherlands
BG	Bulgaria	IT	Italy	NO	Norway
BJ	Benin	JP	Japan	RO	Romania
BR	Brazil	KP	Democratic People's Republic of Korea	SD	Sudan
CF	Central African Republic	KR	Republic of Korea	SE	Sweden
CG	Congo	LI	Liechtenstein	SN	Senegal
CH	Switzerland	LK	Sri Lanka	SU	Soviet Union
CM	Cameroon	LU	Luxembourg	TD	Chad
DE	Germany, Federal Republic of	MC	Monaco	TG	Togo
DK	Denmark	MG	Madagascar	US	United States of America
FI	Finland				

Topical hair growing composition and kit.

In accordance with a first aspect of the invention there is provided a method of enhancing growth of fine vellous hair into terminal hair in an least partially bald person which 5 comprises topically applying to the scalp a compound selected from the group consisting of 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide, 6-chloro-3-(dichloromethyl)-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide, 2-chloro-5-(1-hydroxy-3-oxo-1-10 isoindolinyl)benzene sulfonamide, 3,4-dihydro-3-(phenylmethyl)-6-(trifluoromethyl)-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide, 6-chloro-3-(chloromethyl)-3,4-dihydro-2-methyl-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide, 6-chloro-3,4-dihydro-2-methyl-3-[(2,2,2-trifluoro-15 ethyl)thio]methyl}-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide, 6-chloro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide and 3,4-dihydro-6-trifluoromethyl-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide whereby the smooth muscles in the small blood vessels in the papilla part of 20 connective tissue of skin that supplies the hair follicle is relaxed, thereby increasing blood flow to the hair matrix leading to the maturation of fine hairs into terminal hairs. Thus, the method provides permitting the normal growth of fine vellous hair into terminal hair. According to this aspect of 25 the invention, in one embodiment there is provided a method of permitting the normal growth of fine vellous hair into terminal hair in an least partially bald person in accordance with claim 1, wherein said compound is applied from a topical solution containing at least about 0.01 weight percent said 30 compound in a suitable carrier for said compound.

The total amount of said compound applied each day to the scalp of the patient will vary dependent upon the individual patient. It is contemplated that said compound is administered at least once per day, with one embodiment being 35 twice per day application. The concentration of said compound

is also not critical as it is the total amount of said compound that is important. The suitable solvent serves to place said compound in contact with the bald area, so that ultimately there is only the said compound acting directly on 5 the site to the effected. Because the dosage is topical, essentially 100% of said compound is in direct contact with the area to be treated, so that very low dosages can be used.

In a preferred embodiment the individual dosage will be from about 0.5 to about 2 cc, once or twice per day, at any of 10 the concentration ranges.

In one embodiment of this first aspect of the present invention there is provided a topical solution containing at least about 0.01 weight percent said compound in a suitable carrier for said compound. The total amount of said compound 15 in the suitable carrier may vary greatly, it being understood that it is the total dosage of said compound that is important, and not the total amount of the total solution. To the extent that it is desired not to have too great an amount of said compound applied to any one spot on the scalp, 20 a more dilute solution is preferred so that a larger total volume of fluid is applied to the scalp. The maximum amount of said compound is widely varied and said compound may be present up to the saturation point in the suitable solvent. One preferred embodiment is the provision of at least about 25 0.01% said compound.

In a preferred embodiment of this first aspect of the present invention, said suitable carrier is propylene glycol. In yet another preferred embodiment, said suitable carrier is an ethanolic solution.

30 In a second aspect of the present invention, there is provided a topical medication for reversing the effects of baldness on the scalp of an at least partially bald subject which comprises a baldness-reversing amount of said compound in a form suitable for topical administration in a carrier

therefor, said compound upon continued application to said scalp effecting the growth of hair thereon. In said topical medication said compound is in one embodiment present in an amount of at least about 0.01 weight percent said compound in 5 said suitable carrier for said compound.

In a third aspect of the present invention there is provided a method for reversing the effects of baldness on the scalp of an at least partially bald subject which comprises administering topically to said scalp a baldness-reversing 10 amount of said compound, said compound upon continued application to said scalp effecting the growth of hair thereon. In a preferred embodiment of said method, said compound is applied from a topical solution containing at least about 0.01 weight percent compound in a suitable carrier 15 for said compound.

In a fourth aspect of the present invention there is provided a kit containing a medication suitable for reversing the effects of baldness on the scalp of an at least partially bald subject which comprises a package containing:

- 20 (a) a container including said compound in a form suitable for topical administration to the scalp of said subject; and
- 25 (b) directions for administration of said compound to said scalp for the reversal of the effects of baldness

said compound upon continued application to said scalp effecting the growth of hair thereon. The container may be a standard pharmaceutical container such as a bottle with label 30 directions attached directly to the bottle which explain that said compound which is the active ingredient of the present kit, topical medication and method, is to be topically administered to the scalp of an at least partially bald patient wishing to have hair growth in the bald areas of his

scalp. Alternatively, the container may be a box or other cardboard, plastic or similar container having therein both a package insert with instructions on how to use said compound as a topical baldness treatment together with an inner 5 container of said compound in a suitable solvent therefor.

Baldness generally is due to the failure of the hairs to be permitted to grow into terminal hairs, the large "hair" as laymen understand that term to be. Instead, the fine vellous hair that normally would grow into the terminal hair is 10 essentially precluded from such growth. Said compound acts in the following manner. The smooth muscles in the small blood vessels in the papilla part of connective tissue of skin that supplies the hair follicle are relaxed, thereby increasing blood flow to the hair matrix leading to the maturation of 15 fine hairs into terminal hairs. As a result, there is permitted the maturation of the fine hairs into terminal hairs as would be the case in a normal person without baldness.

EXAMPLE I

20 The compound 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide is described in the literature, including Downing, U.S. patent 3,043,840 (1962), Irons et al., U.S. patent 3,164,588 (1965), de Stevens et al., U.S. patent 3,163,645 (1964), and Jones et al., U.S. patent 25 3,025,292.

The use of 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide is known as a diuretic agent, but never as a topical medication.

Reference has been made herein to 6-chloro-3,4-dihydro-30 2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide. It is to be understood that any derivatives and salt forms of 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide are also contemplated within the scope of the

invention and may be used instead of the 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide.

As this compound has limited solubility in water but has solubility in ethanol, an ethanolic solution is contemplated 5 as a preferred embodiment.

To a graduated 1000 ml beaker there are added first 20 mg powdered 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide and 55 ml 95% ethanol which are intimately mixed together, followed by addition of water to 10 the 1000 ml mark. The resultant solution contains a two percent 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide in a 5% ethanolic solution suitable for topical application to the scalp of a bald patient for the treatment of baldness.

15 For the treatment of baldness, on a daily basis there is administered 2 cc to the scalp of said patient for the growth of hair on said bald spot. Administration is carried on twice a day, once in the morning after showering and once in the evening before retiring.

20 The compound 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide was tested for treating baldness. To test the suitability of 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide as a treatment agent for baldness the following test was conducted.

25 A total of 12 mouse trials were involved. A test was made for 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide on hairless weanling mice on a grading scale of no hair growth ("0"); sparse growth ("1"); fuzzy growth ("2"); and very fuzzy growth ("3"). Six different mice were tested 30 for the compound 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide versus six placebo trials. In the following tabulation, "active ingredient" refers to the compound 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide.

<u>Trial no.</u>	<u>Active Ingredient</u>	<u>Placebo</u>
1	1	3
2	1	2
3	2	2
5	4	2
5	1	1
6	3	1

With the placebo having only one trial hitting the 3 level and two with the 1 level, the trials for 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide show a superior result for the compound of this example versus the placebo.

A standard bottle for pharmaceutical liquids is filled with 200 ml of the solution of this example, and placed in a 15 rectangular cardboard package together with a package insert giving directions for the topical administration of 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide for alleviation of the effects of baldness.

A propylene glycol solution is prepared with 6-chloro-20 3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide in place of the 5% ethanolic solution previously described.

EXAMPLE II

The use of 6-chloro-3-(dichloromethyl)-3,4-dihydro-2H-25 1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide is known as a diuretic and antihypertensive agent, but never as a topical medication.

Reference has been made herein to 6-chloro-3-(dichloromethyl)-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 30 1,1-dioxide. It is to be understood that derivatives and salt forms of 6-chloro-3-(dichloromethyl)-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide are also contemplated within the scope of the invention and may be used instead of the 6-chloro-3-(dichloromethyl)-3,4-dihydro-2H-

1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide. The compound 6-chloro-3-(dichloromethyl)-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide is disclosed in deStevens et al., Experientia, 16, 113 (1960). The compound 5 has a solubility in water of 0.8 mg/ml at 25°C, and a solubility in ethanol of 21 mg/ml at 25°C.

To a graduated 1000 ml beaker there are added first 20 mg powdered 6-chloro-3-(dichloromethyl)-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide and 55 ml 95% 10 ethanol which are intimately mixed together, followed by addition of water to the 1000 ml mark. The resultant solution contains a two percent 6-chloro-3-(dichloromethyl)-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide in a 5% ethanolic solution suitable for topical 15 application to the scalp of a bald patient for the treatment of baldness.

For the treatment of baldness, on a daily basis there is administered 2 cc to the scalp of said patient for the growth of hair on said bald spot. Administration is carried on 20 twice a day, once in the morning after showering and once in the evening before retiring.

50 mg. 6-chloro-3-(dichloromethyl)-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide is dissolved in 1000 ml water to provide a solution for use in treatment of 25 baldness. A standard bottle for pharmaceutical liquids is filled with 200 ml of the solution of this example, and placed in a rectangular cardboard package together with a package insert giving directions for the topical administration of 6-chloro-3-(dichloromethyl)-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide for alleviation of the effects 30 of baldness.

The compound 6-chloro-3-(dichloromethyl)-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide was tested for treating baldness. To test the suitability of 6-chloro-3-

(dichloromethyl)-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide as a treatment agent for baldness the following test was conducted. A total of 12 mouse trials were involved. A test was made for 6-chloro-3-(dichloromethyl)-5 3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide on hairless weanling mice on a grading scale of no hair growth ("0"); sparse growth ("1"); fuzzy growth ("2"); and very fuzzy growth ("3"). Six different mice were tested for the compound 6-chloro-3-(dichloromethyl)-3,4-dihydro-2H-10 1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide versus six placebo trials. In the following tabulation, "active ingredient" refers to the compound 6-chloro-3-(dichloromethyl)-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide.

15	<u>Trial no.</u>	<u>Active Ingredient</u>	<u>Placebo</u>
	1	1	3
	2	1	2
	3	3	2
	4	3	2
20	5	1	1
	6	1	1

With the placebo having only one trial hitting the 3 level and two with the 1 level, the trials for 6-chloro-3-(dichloromethyl)-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide show a superior result for the compound of this example versus the placebo.

A propylene glycol solution is prepared with 6-chloro-3-(dichloromethyl)-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide in place of the previously described 30 5% ethanolic solution.

EXAMPLE III

The compound 2-chloro-5-(1-hydroxy-3-oxo-1-isoindolinyl)benzene sulfonamide is described in the literature.

Reference has been made herein to 2-chloro-5-(1-hydroxy-3-oxo-

1-isoindolinyl)benzene sulfonamide. It is to be understood that any derivatives and salt forms of 2-chloro-5-(1-hydroxy-3-oxo-1-isoindolinyl)benzene sulfonamide are also contemplated within the scope of the invention and may be used instead of 5 the 2-chloro-5-(1-hydroxy-3-oxo-1-isoindolinyl)benzene sulfonamide.

As this compound has limited solubility in water but has solubility in ethanol, an ethanolic solution is contemplated as a preferred embodiment.

10 To a graduated 1000 ml beaker there are added first 20 mg powdered 2-chloro-5-(1-hydroxy-3-oxo-1-isoindolinyl)benzene sulfonamide and 55 ml 95% ethanol which are intimately mixed together, followed by addition of water to the 1000 ml mark. The resultant solution contains a two percent 2-chloro-5-(1-15 hydroxy-3-oxo-1-isoindolinyl)benzene sulfonamide in a 5% ethanolic solution suitable for topical application to the scalp of a bald patient for the treatment of baldness.

For the treatment of baldness, on a daily basis there is administered 2 cc to the scalp of said patient for the growth 20 of hair on said bald spot. Administration is carried on twice a day, once in the morning after showering and once in the evening before retiring.

A standard bottle for pharmaceutical liquids is filled with 200 ml of the solution of this example, and placed in a 25 rectangular cardboard package together with a package insert giving directions for the topical administration of 2-chloro-5-(1-hydroxy-3-oxo-1-isoindolinyl)benzene sulfonamide for alleviation of the effects of baldness.

The compound 2-chloro-5-(1-hydroxy-3-oxo-1-isoindolinyl)benzene sulfonamide was tested for treating baldness. To 30 test the suitability of 2-chloro-5-(1-hydroxy-3-oxo-1-isoindolinyl)benzene sulfonamide as a treatment agent for baldness the following test was conducted. A total of 12 mouse trials were involved. A test was made for 2-chloro-5-

(1-hydroxy-3-oxo-1-isoindolinyl)benzene sulfonamide on hairless weanling mice on a grading scale of no hair growth ("0"); sparse growth ("1"); fuzzy growth ("2"); and very fuzzy growth ("3"). Six different mice were tested for the compound 5 2-chloro-5-(1-hydroxy-3-oxo-1-isoindolinyl)benzene sulfonamide versus six placebo trials. In the following tabulation, "active ingredient" refers to the compound 2-chloro-5-(1-hydroxy-3-oxo-1-isoindolinyl)benzene sulfonamide.

<u>Trial no.</u>	<u>Active Ingredient</u>	<u>Placebo</u>
10	1	3
	2	1
	3	2
	4	2
	5	1
15	6	1

With the placebo having only one trial hitting the 3 level and two with the 1 level, the trials for 2-chloro-5-(1-hydroxy-3-oxo-1-isoindolinyl)benzene sulfonamide show a superior result for the compound of this example versus the 20 placebo.

A propylene glycol solution is prepared with 2-chloro-5-(1-hydroxy-3-oxo-1-isoindolinyl)benzene sulfonamide in place of the 5% ethanolic solution.

EXAMPLE IV

25 Synthesis of 3,4-dihydro-3-(phenylmethyl)-6-(trifluoromethyl)-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide is disclosed in Holdrege et al., J. Am. Chem. Soc., 81, 4807 (1959); and Goldberg, U.S. patent 3,265,573 (1966).

The use of 3,4-dihydro-3-(phenylmethyl)-6-(trifluoromethyl)-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide is 30 known as a diuretic and antihypertensive agent, but never as a topical medication.

Reference has been made herein to 3,4-dihydro-3-(phenylmethyl)-6-(trifluoromethyl)-2H-1,2,4-benzothiadiazine-7-

sulfonamide 1,1-dioxide. It is to be understood that derivatives and salt forms of 3,4-dihydro-3-(phenylmethyl)-6-(trifluoromethyl)-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide are also contemplated within the scope of the 5 invention and may be used instead of the 3,4-dihydro-3-(phenylmethyl)-6-(trifluoromethyl)-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide.

The compound is not soluble in water but is soluble in alcohols, making an ethanolic solution a preferred embodiment 10 of the present invention.

To a graduated 1000 ml beaker there are added first 20 mg powdered 3,4-dihydro-3-(phenylmethyl)-6-(trifluoromethyl)-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide and 55 ml 95% ethanol which are intimately mixed together, followed by 15 addition of water to the 1000 ml mark. The resultant solution contains a two percent 3,4-dihydro-3-(phenylmethyl)-6-(trifluoromethyl)-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide in a 5% ethanolic solution suitable for topical application to the scalp of a bald patient for the treatment 20 of baldness.

For the treatment of baldness, on a daily basis there is administered 2 cc to the scalp of said patient for the growth of hair on said bald spot. Administration is carried on twice a day, once in the morning after showering and once in 25 the evening before retiring.

A standard bottle for pharmaceutical liquids is filled with 200 ml of the solution and placed in a rectangular cardboard package together with a package insert giving directions for the topical administration of 3,4-dihydro-3-(phenylmethyl)-6-(trifluoromethyl)-2H-1,2,4-benzothiadiazine-30 7-sulfonamide 1,1-dioxide for alleviation of the effects of baldness.

The compound 3,4-dihydro-3-(phenylmethyl)-6-(trifluoromethyl)-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide

was tested for treating baldness. To test the suitability of 3,4-dihydro-3-(phenylmethyl)-6-(trifluoromethyl)-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide as a treatment agent for baldness the following test was conducted. A total of 12 mouse trials were involved. A test was made for 3,4-dihydro-3-(phenylmethyl)-6-(trifluoromethyl)-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide on hairless weanling mice on a grading scale of no hair growth ("0"); sparse growth ("1"); fuzzy growth ("2"); and very fuzzy growth ("3"). Six different mice were tested for the compound 3,4-dihydro-3-(phenylmethyl)-6-(trifluoromethyl)-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide versus six placebo trials. In the following tabulation, "active ingredient" refers to the compound 3,4-dihydro-3-(phenylmethyl)-6-(trifluoromethyl)-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide.

<u>Trial no.</u>	<u>Active Ingredient</u>	<u>Placebo</u>
1	3	3
2	1	2
20 3	1	2
4	1	2
5	3	/
6	3	/
		1

With the placebo having only one trial hitting the 3 level and two with the 1 level, the trials for 3,4-dihydro-3-(phenylmethyl)-6-(trifluoromethyl)-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide show a superior result for the compound of this example versus the placebo.

A propylene glycol solution is prepared with 3,4-dihydro-3-(phenylmethyl)-6-(trifluoromethyl)-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide in place of the 95% ethanolic solution.

EXAMPLE V

Synthesis of 6-chloro-3-(chloromethyl)-3,4-dihydro-2-methyl-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide is disclosed in Close et al., J. Am. Chem. Soc., 82, 1132 (1960). The use of 6-chloro-3-(chloromethyl)-3,4-dihydro-2-methyl-2H-5 1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide is known as a diuretic and antihypertensive agent, but never as a topical medication.

Reference has been made herein to 6-chloro-3-(chloromethyl)-3,4-dihydro-2-methyl-2H-1,2,4-benzothiadiazine-7-10 sulfonamide 1,1-dioxide. It is to be understood that any derivatives and salt forms of 6-chloro-3-(chloromethyl)-3,4-dihydro-2-methyl-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide are also contemplated within the scope of the invention and may be used instead of the 6-chloro-3-(chloromethyl)-3,4-dihydro-2-methyl-2H-1,2,4-benzothiadiazine-7-15 sulfonamide 1,1-dioxide.

The compound 6-chloro-3-(chloromethyl)-3,4-dihydro-2-methyl-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide is sparingly soluble in ethanol, and almost insoluble in water.

20 To a graduated 1000 ml beaker there are added first 20 mg powdered 6-chloro-3-(chloromethyl)-3,4-dihydro-2-methyl-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide and 55 ml 95% ethanol which are intimately mixed together, followed by addition of water to the 1000 ml mark. The resultant 25 solution contains a two percent 6-chloro-3-(chloromethyl)-3,4-dihydro-2-methyl-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide in a 5% ethanolic solution suitable for topical application to the scalp of a bald patient for the treatment of baldness.

30 For the treatment of baldness, on a daily basis there is administered 2 cc to the scalp of said patient for the growth of hair on said bald spot. Administration is carried on twice a day, once in the morning after showering and once in the evening before retiring.

A standard bottle for pharmaceutical liquids is filled with 200 ml of the above solution, and placed in a rectangular cardboard package together with a package insert giving directions for the topical administration of 6-chloro-3-5 (chloromethyl)-3,4-dihydro-2-methyl-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide for alleviation of the effects of baldness.

The compound 6-chloro-3-(chloromethyl)-3,4-dihydro-2-methyl-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide was 10 tested for treating baldness. To test the suitability of 6-chloro-3-(chloromethyl)-3,4-dihydro-2-methyl-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide as a treatment agent for baldness the following test was conducted. A total of 12 mouse trials were involved. A test was made for 6-15 chloro-3-(chloromethyl)-3,4-dihydro-2-methyl-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide on hairless weanling mice on a grading scale of no hair growth ("0"); sparse growth ("1"); fuzzy growth ("2"); and very fuzzy growth ("3"). Six different mice were tested for the compound 6-20 chloro-3-(chloromethyl)-3,4-dihydro-2-methyl-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide versus six placebo trials. In the following tabulation, "active ingredient" refers to the compound 6-chloro-3-(chloromethyl)-3,4-dihydro-2-methyl-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide.

25	<u>Trial no.</u>	<u>Active Ingredient</u>	<u>Placebo</u>
	1	1	3
	2	3	2
	3	2	2
	4	2	2
30	5	3	1
	6	3	1

With the placebo having only one trial hitting the 3 level and two with the 1 level, the trials for 6-chloro-3-(chloromethyl)-3,4-dihydro-2-methyl-2H-1,2,4-benzothiadiazine-

7-sulfonamide 1,1-dioxide show a superior result for the compound of this example versus the placebo.

A propylene glycol solution is prepared with 6-chloro-3-(chloromethyl)-3,4-dihydro-2-methyl-2H-1,2,4-benzothiadiazine-5 7-sulfonamide 1,1-dioxide in place of the 5% ethanolic solution.

EXAMPLE VI

Synthesis of 6-chloro-3,4-dihydro-2-methyl-3-{{(2,2,2-trifluoroethyl)thio}methyl}-2H-1,2,4-benzothiadiazine-7-10 sulfonamide 1,1-dioxide is disclosed in McManus, U.S. Patent 3,009,911 (1961). The use of 6-chloro-3,4-dihydro-2-methyl-3-{{(2,2,2-trifluoroethyl)thio}methyl}-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide is known as a diuretic and antihypertensive agent, but never as a topical 15 medication.

Reference has been made herein to 6-chloro-3,4-dihydro-2-methyl-3-{{(2,2,2-trifluoroethyl)thio}methyl}-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide. It is to be understood that derivatives and salt forms of 6-chloro-3,4-dihydro-2-methyl-3-{{(2,2,2-trifluoroethyl)thio}methyl}-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide are also contemplated within the scope of the invention and may be used instead of the 6-chloro-3,4-dihydro-2-methyl-3-{{(2,2,2-trifluoroethyl)thio}methyl}-2H-1,2,4-benzothiadiazine-7-25 sulfonamide 1,1-dioxide. It is desirable to include in any aqueous medium alkali metal carbanates or hydroxides because the compound 6-chloro-3,4-dihydro-2-methyl-3-{{(2,2,2-trifluoroethyl)thio}methyl}-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide is practically insoluble in water 30 without this adjustment.

To a graduated 1000 ml beaker there are added first 20 mg powdered 6-chloro-3,4-dihydro-2-methyl-3-{{(2,2,2-trifluoroethyl)thio}methyl}-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide and 55 ml 95% ethanol which are intimately mixed

together, followed by addition of water to the 1000 ml mark. The resultant solution contains a two percent 6-chloro-3,4-dihydro-2-methyl-3-[(2,2,2-trifluoroethyl)thio]methyl]-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide in a 5% 5 ethanolic solution suitable for topical application to the scalp of a bald patient for the treatment of baldness.

For the treatment of baldness, on a daily basis there is administered 2 cc to the scalp of said patient for the growth of hair on said bald spot. Administration is carried on 10 twice a day, once in the morning after showering and once in the evening before retiring.

50 mg 6-chloro-3,4-dihydro-2-methyl-3-[(2,2,2-trifluoroethyl)thio]methyl]-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide is dissolved in 1000 ml water having 15 added thereto magnesium carbonate to provide a solution for use in treatment of baldness in accordance with this example.

A standard bottle for pharmaceutical liquids is filled with 200 ml of the solution of this example, and placed in a rectangular cardboard package together with a package insert 20 giving directions for the topical administration of 6-chloro-3,4-dihydro-2-methyl-3-[(2,2,2-trifluoroethyl)thio]methyl]-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide for alleviation of the effects of baldness.

A propylene glycol solution is prepared with 6-chloro-25 3,4-dihydro-2-methyl-3-[(2,2,2-trifluoroethyl)thio]methyl]-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide in place of the 95% ethanolic solution.

EXAMPLE VII

The compound 6-chloro-2H-1,2,4-benzothiadiazine-7-30 sulfonamide 1,1-dioxide is described in the literature, including Downing, U.S. patent 3,043,840 (1962), Irons et al., U.S. patent 3,164,588 (1965), de Stevens et al., U.S. patent 3,163,645 (1964), and Jones et al., U.S. patent 3,025,292.

The use of 6-chloro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide is known as a diuretic agent, but never as a topical medication.

Reference has been made herein to 6-chloro-2H-1,2,4-5 benzothiadiazine-7-sulfonamide 1,1-dioxide. It is to be understood that any derivatives and salt forms of 6-chloro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide are also contemplated within the scope of the invention and may be used instead of the 6-chloro-2H-1,2,4-benzothiadiazine-7-10 sulfonamide 1,1-dioxide.

As this compound has limited solubility in water but has solubility in ethanol, an ethanolic solution is contemplated as a preferred embodiment.

To a graduated 1000 ml beaker there are added first 20 mg 15 powdered 6-chloro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide and 55 ml 95% ethanol which are intimately mixed together, followed by addition of water to the 1000 ml mark.

The resultant solution contains a two percent 6-chloro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide in a 5% 20 ethanolic solution suitable for topical application to the scalp of a bald patient for the treatment of baldness.

For the treatment of baldness, on a daily basis there is administered 2 cc to the scalp of said patient for the growth of hair on said bald spot. Administration is carried on 25 twice a day, once in the morning after showering and once in the evening before retiring.

A standard bottle for pharmaceutical liquids is filled with 200 ml of the solution of this example, and placed in a rectangular cardboard package together with a package insert 30 giving directions for the topical administration of 6-chloro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide for alleviation of the effects of baldness.

The compound 6-chloro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide was tested for treating baldness. To

test the suitability of 6-chloro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide as a treatment agent for baldness the following test was conducted. A total of 12 mouse trials were involved. A test was made for 6-chloro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide on hairless weanling mice on a grading scale of no hair growth ("0"); sparse growth ("1"); fuzzy growth ("2"); and very fuzzy growth ("3"). Six different mice were tested for the compound 6-chloro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide versus six placebo trials. In the following tabulation, "active ingredient" refers to the compound 6-chloro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide.

<u>Trial no.</u>	<u>Active Ingredient</u>	<u>Placebo</u>
15	1	3
	2	2
	3	2
	4	2
	5	1
	6	1

20 With the placebo having only one trial hitting the 3 level and two with the 1 level, the trials for 6-chloro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide show a superior result for the compound of this example versus the placebo.

25 A propylene glycol solution is prepared with 6-chloro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide in place of the 5% ethanolic solution.

EXAMPLE VIII

Testing of the compound 3,4-dihydro-6-trifluoromethyl-2H-30 1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide is provided in this example. To a graduated 1000 ml beaker there are added first 20 mg powdered 3,4-dihydro-6-trifluoromethyl-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide and 55 ml 95% ethanol which are intimately mixed together, followed by

addition of water to the 1000 ml mark. The resultant solution contains a two percent 3,4-dihydro-6-trifluoromethyl-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide in a 5% ethanolic solution suitable for topical application to the 5 scalp of a bald patient for the treatment of baldness.

For the treatment of baldness, on a daily basis there is administered 2 cc to the scalp of said patient for the growth of hair on said bald spot. Administration is carried on twice a day, once in the morning after showering and once in the 10 evening before retiring.

50 mg 3,4-dihydro-6-trifluoromethyl-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide is dissolved in 1000 ml water having added thereto magnesium carbonate to provide a solution for use in treatment of baldness in accordance with 15 this example.

A standard bottle for pharmaceutical liquids is filled with 200 ml of the solution of this example, and placed in a rectangular cardboard package together with a package insert giving directions for the topical administration of 3,4-20 dihydro-6-trifluoromethyl-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide for alleviation of the effects of baldness.

The compound 3,4-dihydro-6-trifluoromethyl-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide was tested for 25 treating baldness. To test the suitability of 3,4-dihydro-6-trifluoromethyl-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide as a treatment agent for baldness the following test was conducted. A total of 12 mouse trials were involved. A test was made for 3,4-dihydro-6-trifluoromethyl-2H-1,2,4-30 benzothiadiazine-7-sulfonamide 1,1-dioxide on hairless weanling mice on a grading scale of no hair growth ("0"); sparse growth ("1"); fuzzy growth ("2"); and very fuzzy growth ("3"). Six different mice were tested for the compound 3,4-dihydro-6-trifluoromethyl-2H-1,2,4-benzothiadiazine-7-

sulfonamide 1,1-dioxide versus six placebo trials. In the following tabulation, "active ingredient" refers to the compound 3,4-dihydro-6-trifluoromethyl-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide

	<u>Trial no.</u>	<u>Active Ingredient</u>	<u>Placebo</u>
	1	2	3
	2	2	2
	3	2	2
	4	3	2
10	5	1	1
	6	3	1

With the placebo having only one trial hitting the 3 level and two with the 1 level, the trials for 3,4-dihydro-6-trifluoromethyl-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide show a superior result for the compound of this example versus the placebo.

A propylene glycol solution is prepared with 3,4-dihydro-6-trifluoromethyl-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide in place of the 95% ethanolic solution.

WHAT IS CLAIMED IS:

1. A method of enhancing growth of fine vellous hair into terminal hair in an least partially bald person which comprises topically applying to the scalp a compound selected 5 from the group consisting of 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide, 6-chloro-3-(di-chloromethyl)-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide, 2-chloro-5-(1-hydroxy-3-oxo-1-isoindolinyl)benzene sulfonamide, 3,4-dihydro-3-(phenyl-10 methyl)-6-(trifluoromethyl)-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide, 6-chloro-3-(chloromethyl)-3,4-dihydro-2-methyl-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide, 6-chloro-3,4-dihydro-2-methyl-3-[(2,2,2-trifluoroethyl)thio]methyl}-2H-1,2,4-benzothiadiazine-7-sulfonamide 15 1,1-dioxide, 6-chloro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide and 3,4-dihydro-6-trifluoromethyl-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide whereby the smooth muscles in the small blood vessels in the papilla part of connective tissue of skin that supplies the hair follicle is 20 relaxed, thereby increasing blood flow to the hair matrix leading to the maturation of fine hairs into terminal hairs.

2. A method of permitting the normal growth of fine vellous hair into terminal hair in an least partially bald person in accordance with claim 1, wherein said compound is 25 applied from a topical solution containing at least about 0.01 weight percent said compound in a suitable carrier for said compound.

3. A method of permitting the normal growth of fine vellous hair into terminal hair in an least partially bald 30 person in accordance with claim 2, wherein said suitable carrier is propylene glycol.

4. A method of permitting the normal growth of fine vellous hair into terminal hair in an least partially bald person in accordance with claim 2, wherein said suitable 35 carrier is an ethanolic solution.

5. A method of permitting the normal growth of fine vellous hair into terminal hair in an least partially bald person in accordance with claim 2, wherein the solvent is a mixture of ethylene glycol and propylene glycol.

5 6. A method of claim 1 wherein said compound is 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide.

7. A method of claim 1 wherein said compound is 6-chloro-3-(dichloromethyl)-3,4-dihydro-2H-1,2,4-benzothia-10 diazine-7-sulfonamide 1,1-dioxide.

8. A method of claim 1 wherein said compound is 2-chloro-5-(1-hydroxy-3-oxo-1-isoindolinyl)benzene sulfonamide.

9. A method of claim 1 wherein said compound is 3,4-dihydro-3-(phenylmethyl)-6-(trifluoromethyl)-2H-1,2,4-15 benzothiadiazine-7-sulfonamide 1,1-dioxide.

10. A method of claim 1 wherein said compound is 6-chloro-3-(chloromethyl)-3,4-dihydro-2-methyl-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide.

11. A method of claim 1 wherein said compound is 6-20 chloro-3,4-dihydro-2-methyl-3-{{(2,2,2-trifluoroethyl)thio)methyl}-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide.

12. A method of claim 1 wherein said compound is 6-chloro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide.

25 13. A method of claim 1 wherein said compound is 3,4-dihydro-6-trifluoromethyl-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide.

14. A topical medication for reversing the effects of baldness on the scalp of an at least partially bald subject 30 which comprises a baldness-reversing amount of a compound of claim in a form suitable for topical administration in a carrier therefor, said compound on continued application to said scalp effecting the growth of hair thereon.

15. A topical medication of claim 14 wherein said compound is present in an amount of at least about 0.01 weight percent in said suitable carrier.

16. A method for reversing the effects of baldness on 5 the scalp of an at least partially bald subject which comprises administering topically to said scalp a baldness-reversing amount of a compound of claim 1.

17. A kit containing a medication suitable for reversing the effects of baldness on the scalp of an at least partially 10 bald subject which comprises a package containing:

- (a) a container including a topical medication containing a compound of claim 1 for topical administration to the scalp of said subject; and
- 15 (b) directions for administration of said compound to said scalp for the reversal of the effects of baldness said compound upon continued application to said scalp effecting the growth of hair thereon.

20 18. A kit of claim 17 wherein said compound in said container (a) includes a topical solution containing at least about 0.01 weight percent said compound in a carrier suitable therefor.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 87/01575

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) *

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC⁴: A 61 K 7/06; A 61 K 31/54; A 61 K 31/40

II. FIELDS SEARCHED

Minimum Documentation Searched *

Classification System	Classification Symbols
IPC ⁴	A 61 K

Documentation Searched other than Minimum Documentation
to the Extent that such Documents are included in the Fields Searched *

III. DOCUMENTS CONSIDERED TO BE RELEVANT *

Category *	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
X, Y	The Merck Index, 10th edition, 1983, Merck & Co., Inc., (Rahway, N.J., US), see page 147, no. 1036; pages 305-306, 14-18 no. 2143, page 310, no. 2171; pages 692-693, no. 4683; pages 694-695, no. 4695; page 863, no. 5883; page 1095, no. 7457; page 1376, no. 9437 --	
X	US, A, 3476858 (NELSON et al.) 4 November 1968 see column 6, example 5	14-18
X	EP, A, 0125420 (BOEHRINGER INGELHEIM LTD) 21 November 1984 see page 11, lines 24-26	14-18
Y	EP, A, 0027655 (WELLA AG) 29 April 1981 see the whole document, in particular page 2, line 6 - page 3, line 11 --	14-18
Y	US, A, 4184039 (SOLDATI et al.) 15 January 1980	./.

* Special categories of cited documents: *
 "A" document defining the general state of the art which is not
 considered to be of particular relevance
 "E" earlier document but published on or after the international
 filing date
 "L" document which may throw doubts on priority claim(s) or
 which is cited to establish the publication date of another
 citation or other special reason (as specified)
 "O" document referring to an oral disclosure, use, exhibition or
 other means
 "P" document published prior to the international filing date but
 later than the priority date claimed

"T" later document published after the international filing date
 or priority date and not in conflict with the application but
 cited to understand the principle or theory underlying the
 invention
 "X" document of particular relevance; the claimed invention
 cannot be considered novel or cannot be considered to
 involve an inventive step
 "Y" document of particular relevance; the claimed invention
 cannot be considered to involve an inventive step when the
 document is combined with one or more other such docu-
 ments, such combination being obvious to a person skilled
 in the art
 "&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search

21st August 1987

International Searching Authority

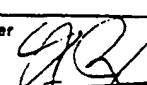
EUROPEAN PATENT OFFICE

Date of Mailing of this International Search Report

- 2 OCT 1987

Signature of Authorized Officer

L. ROSSI



FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

see the whole document

14-18

V. OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE:

This International search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. Claim numbers 1-13 because they relate to subject matter not required to be searched by this Authority, namely:

See PCT Rule 39.1(iv) Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

2. Claim numbers because they relate to parts of the International application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. Claim numbers because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING:

This International Searching Authority found multiple inventions in this International application as follows:

1. As all required additional search fees were timely paid by the applicant, this International search report covers all searchable claims of the International application.

2. As only some of the required additional search fees were timely paid by the applicant, this International search report covers only those claims of the International application for which fees were paid, specifically claims:

3. No required additional search fees were timely paid by the applicant. Consequently, this International search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

The additional search fees were accompanied by applicant's protest.
 No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON

INTERNATIONAL APPLICATION NO. PCT/US 87/01575 (SA 17849)

This Annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 10/09/87

The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A- 3476858	04/11/69	None	
EP-A- 0125420	21/11/84	AU-A- 2569684 JP-A- 59176212 CA-A- 1212329 AU-B- 562929	20/09/84 05/10/84 07/10/86 25/06/87
EP-A- 0027655	29/04/81	DE-A- 2942666 JP-A- 56065811 AT-B- E6464	07/05/81 03/06/81 15/03/84
US-A- 4184039	15/01/80	None	